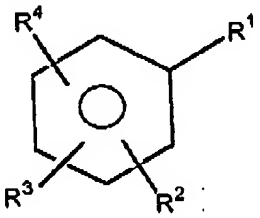
6,416,779).

Claim 1 is directed to an exoprotein inhibitor for inhibiting the production of exoproteins from Gram positive bacteria in and around a vagina. The exoprotein inhibitor comprises a non-absorbent substrate for insertion into the vagina being selected from the group consisting of a non-absorbent incontinence device, a barrier birth control device, a tampon applicator, and a douche. The non-absorbent substrate has deposited thereon an effective amount of a first active ingredient having the general formula:



wherein R^1 is $-OR^6OH$; R^6 is a divalent saturated or unsaturated aliphatic hydrocarbyl moiety; R^2, R^3, and R^4 are independently selected from the group consisting of H, OH, COOH, and $-C(O)R^9$; R^9 is hydrogen or a monovalent saturated or unsaturated aliphatic hydrocarbyl moiety, wherein the first active ingredient is effective in inhibiting the production of exoprotein from Gram positive bacteria.

Stolar discloses an antibacterial pharmaceutical composition to treat bacterial infections comprising effective amounts of a combination of phenoxyethanol, trimethoprim, and an antibacterial sulfa drug. The composition is for internal administration, and can be distributed in a pharmaceutically

acceptable carrier. Examples of suitable carriers include sugar, dextrin, dextrose, sodium chloride, and the like.[1]

Stolar fails to disclose a non-absorbent substrate for insertion into the vagina being selected from the group consisting of a non-absorbent incontinence device, a barrier birth control device, a tampon applicator, and a douche. In an attempt to find each and every element of claim 1 as required by the M.P.E.P. for a determination of *prima facie* obviousness, the Office cites the D'Augustine et al. reference for combination with Stolar.

D' Augustine et al. disclose devices, methods, and compositions for treating vaginal fungal, bacterial, viral, and parasitic infections by intravaginal or transvaginal administration of therapeutic and/or palliative antifungal, antibacterial, antiviral or parasiticidal drugs to the vagina or to the uterus. Specifically, a device such as a tampon, tampon-like device, vaginal ring, pessary, cervical cup, vaginal sponge, intravaginal tablet, or intravaginal suppository, delivers the drug, which can be in the form of a paste, cream, ointment, microcapsule, solution, powder, or gel having a sufficient thickness to maintain prolonged vaginal epithelium and mucosa contact. In one embodiment, the drug can be incorporated into a cream, lotion, foam, paste, ointment, or gel which can be applied to the vagina using an applicator.[2]

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[1] Applicants note that, as discussed in more detail below, Stolar does not disclose phenoxyethanol as an antibacterial agent; he only describes phenoxyethanol as a single component of a three-component antibacterial composition. Stolar fails to disclose that phenoxyethanol alone has antibacterial properties.
[2] D' Augustine et al. at column 18, lines 24-26.

In order for the Office to show a *prima facie* case of obviousness, M.P.E.P. §2143 requires that the Office must meet three criteria: (1) the prior art references must teach or suggest all of the claim limitations; (2) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the references, and (3) there must be some reasonable expectation of success. The Office has failed to meet its burden under (2) above, as there is no motivation or suggestion to combine the Stolar and D' Augustine et al. references to arrive at Applicants' claim 1.

The Office asserts in the previous Office action that, as Stolar teaches phenoxyethanol as an effective antibacterial agent and D'Augustine discloses effective delivery of antibacterial compounds through non-absorbent vaginal devices, it would have been obvious for one skilled in the art at the time of the instant invention to add the phenoxyethanol of Stolar to the non-absorbent devices of D'Augustine for treating microbial or bacterial infections in the vaginal area. Applicants respectfully disagree, and submit that the Office is misinterpreting the Stolar reference.

The Office has stated that since Stolar suggests including a synergistically effective amount of phenyxoethanol in the "antibacterial composition," this implies that phenoxyethanol has antibacterial properties. However, as noted above, Stolar does not disclose phenoxyethanol as an antibacterial agent. Rather, phenoxyethanol is described merely as a single component of a three-component composition, wherein the composition has antibacterial properties. There is, however, no disclosure that

phenoxyethanol alone has any antibacterial properties, much less that phenoxyethanol is effective in inhibiting the production of exoprotein from Gram positive bacteria.

Rather, Stolar merely discloses that when added to a composition comprising a sulfa drug and trimethoprim, phenoxyethanol synergistically increases the antibacterial activity of the composition. This disclosure, however, is not a suggestion or teaching as to the antimicrobial effect of phenoxyethanol in the absence of trimethoprim and a sulfa drug. In fact, Stolar explicitly teaches that phenoxyethanol will not act synergistically with just any combination of drugs, but rather only states that the synergistic effect occurs when phenoxyethanol is combined with a sulfa drug and trimethoprim. For instance, Stolar states at column 1, lines 58-61 that synergistic activity is not observed when phenoxyethanol is added to either the sulfa drug alone or the trimethoprim alone.[3]

Furthermore, Stolar actually teaches that phenoxyethanol is not an effective antibacterial (for internal administration) when administered in the absence of a sulfa drug and trimethoprim. For instance, in Example 6, Stolar evaluates the effectiveness of compositions comprising a combination of a sulfa drug, trimethoprim, and phenoxyethanol, compositions comprising two of the three drugs, or compositions comprising only a sulfa drug, trimethoprim, or phenoxyethanol when the

[3] "It has surprisingly been found that when phenoxyethanol is added to a mixture of a sulfa drug and trimethoprim that the synergistic activity of the overall composition is increased to an unexpected extent. This is most surprising in view of the fact that when phenoxyethanol is added to either the sulfa drug alone or the trimethoprim alone, no such activity is observed." Stolar at col. 1, ln. 55-61.

compositions are administered orally to chicks.[4] The results show that of the eight chicks administered phenoxyethanol alone, none were cured, and seven of the eight were either sick or died.

In light of the foregoing, applicants submit that there is no motivation in the cited references to incorporate phenoxyethanol into the devices of D'Augustine to treat microbial or bacterial infections in the vaginal area. In particular, why would one skilled in the art pick phenoxyethanol from the three-drug cocktail disclosed in Stolar to incorporate into the devices of D'Augustine, given the teaching in Stolar that phenoxyethanol is not an effective antimicrobial when used in the absence of the sulfa drug and trimethoprim? One skilled in the art could not and would not be so motivated.

Furthermore, the Stolar reference is directed to antibacterial compositions suitable for administration, particularly oral administration, to treat bacterial infections in humans and animals. For example, as noted above, in Example 6 chicks were orally treated for *Escherichia coli* (*E. coli*) infection by mixing the Stolar antibacterial composition with the chicks' drinking water. As such, why would one skilled in the art look to the Stolar antibacterial, orally-administered

[4] In Example 6 of Stolar, chicks were given 300 ml of water containing one of the compositions, and on the following day were given an injection of 0.5 ml suspension of 2 x 10^6 organisms of E. coli in 5% mucin solution. The chicks were also given another treatment of the medication. The treatment was continued for 2 more days post infection. The severity and presence or lack of infection in each chick was recorded as of the 11th day post inoculation. The chicks were categorized as either "cured," "slightly sick," "sick," or "dead," with "cured" and "slightly sick" being considered as one group and "sick" and "dead" being considered as another group. Stolar at col. 4, ln. 30 to col. 5, ln. 3.

composition over any other antibacterial compositions for use in the intravaginal devices of D' Augustine et al.? Nowhere in Stolar is it disclosed to use the antibacterial composition for the treatment of vaginal fungal, bacterial, viral, and parasitic infections.[5]

Additionally, even assuming that phenoxyethanol is disclosed as an antibacterial as suggested by the Office, why would one skilled in the art pick Stolar's composition over all of the other non-toxic, antibacterial compositions present in the art, particularly when D'Augustine et al. provide numerous suitable antibacterial compositions to use with their non-

[5] The Office states that Stolar teaches solutions and suppositories as well as tablets, thus suggesting other routes of administration, rendering moot the idea that an oral composition cannot be combined with non-absorbent devices. Applicants respectfully disagree. As noted above, there is no disclosure or suggestion in Stolar that the compositions described therein could be used to treat vaginal infections. Furthermore, the disclosure in Stolar of routes of administration other than tablets does not amount to motivation to incorporate the compositions of Stolar into a non-absorbent substrate for insertion into a vagina. As mentioned in applicants' specification and shown in the examples, the first active ingredient used in the exoprotein inhibitor of claim 1 of the present invention is not acting as an antimicrobial agent as apparently understood by the Office. As mentioned in Applicants' specification, the first active ingredient acts to **inhibit the production of exoproteins** from Gram positive bacteria, but does not seek to kill the bacteria as the killing of bacteria is non-selective and the "good" bacteria needed to maintain a healthy vagina would also be killed. Thus, the non-selective killing of bacteria could actually be very harmful to the vagina and could cause serious health problems. This is significant. The first active ingredient as claimed in claim 1 of the present invention actually seeks not to act as an antimicrobial agent as claimed by the Office, but seeks to only prevent the production of potentially harmful by-products of bacteria, while allowing the bacteria to live. It is also noted that none of the cited references suggest or disclose that a composition having the general formula of the first active ingredient of claim 1 can act in such a manner. Since not all antimicrobial agents are suitable for use in a vagina, in the absence of any teaching or suggestion that the compositions of Stolar are suitable for use in a vaginal environment, the mere disclosure in Stolar of routes of administration such as solutions and suppositories does not amount to a teaching or suggestion to use the Stolar composition in a vaginal environment.

absorbent devices and do not point to any need for alternatives? D' Augustine et al. simply teach compositions that can be used as antibacterials to treat bacterial infections of the vagina and devices for delivering the compositions; and even provide several commercially acceptable antibacterial compositions. The D' Augustine et al. reference fails to provide a reason why one skilled in the art would choose another antibacterial over those listed in the D' Augustine et al. reference or disclosed elsewhere in the art. Nor does Stolar provide such motivation since, as discussed above, there is no disclosure or suggestion in Stolar to use the antibacterial composition for the treatment of vaginal fungal, bacterial, viral, and parasitic infections.

Furthermore, the D'Augustine et al. reference is directed to treating infections such as *Haemophilus vaginitus* and *Corenebacterium vaginitis* caused by anaerobic bacteria such as *Gardnerella vaginalis* or *Mycoplasma huminus*. No where in the D'Augustine et al. reference are infections caused by *Eschericia coli* taught or suggested. As such, one skilled in the art would not, and could not, be motivated to use the antibacterial three-drug composition of Stolar, which, as shown in the working Examples is effective against *Eschericia coli*, over the antibacterials discussed in the D'Augustine et al. reference directed to treating the infections caused by *Gardnerella vaginalis* or *Mycoplasma huminus*. More particularly, *Eschericia coli* is a **gram-negative bacterium**. As such, one skilled in the art reading the Stolar and D'Augustine et al. references would not and could not be motivated to use the antibacterial three-drug composition of Stolar, shown to be effective against gram-negative bacteria, for treatments caused by the gram-positive

bacteria, *Gardnerella vaginalis* or *Mycoplasma huminus*, let alone the gram-positive bacteria of Applicants' claimed invention.

With all due respect, it appears that the Office has used impermissible hindsight analysis and reconstruction when combining the Stolar and D' Augustine et al. references to arrive at Applicants' claim 1. Notably, it would be clear to one skilled in the art reading D' Augustine et al. that an antibacterial composition could be used to treat bacterial vaginal infections. There are, however, a myriad of antibacterial compositions, many of which are used to treat vaginal infections. What is important is that there is no motivation or suggestion to use the compositions of Stolar over any of the other enormous number of antibacterial compositions described in the art, which are suitable for use in a vagina.

As there is no motivation or suggestion to combine the Stolar and D' Augustine et al. references to arrive at each and every limitation of claim 1, claim 1 is patentable over Stolar in view of D'Augustine et al.

Claims 2-4 and 6-10 depend directly or indirectly on claim 1. As such, claims 2-4 and 6-10 are patentable for the same reasons as claim 1 set forth above, as well as for the additional elements they require.

2. Rejection of Claims 1-4, 6-11, and 14-25 for Obviousness Type Double Patenting

Claims 1-4, 6-11, and 14-25 have been rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of Syverson, et al. (U.S.

Patent No. 6,821,999) in view of any one of Syverson (U.S. Patent No. 5,612,045), Syverson (U.S. Patent No. 5,685,872), or Syverson (U.S. Patent No. 5,618,554). In response thereto, Applicants have enclosed herewith a Terminal Disclaimer in accordance with 37 C.F.R. 1.321(c) to obviate the rejection. Accordingly, Applicants respectfully request the obviousness-type double patenting rejection be withdrawn.

3. Rejection of Claims 14-25 Under 35 U.S.C. §103(a)

Reconsideration is requested of the rejection of claims 14-25 under 35 U.S.C. §103(a) as being unpatentable over of Stolar (U.S. 4,470,978) in view of D' Augustine et al. (U.S. 6,416,779) and Syverson (U.S. 5,612,045).

Claims 14-25 depend from claim 1 and further require the exoprotein inhibitor to comprise an effective amount of a second active ingredient having the general formula: R^{10}–O–R^{11}, wherein R^{10} is a straight or branched alkyl or straight or branched alkenyl having from 8 to about 18 carbon atoms and R^{11} is selected from the group consisting of an alcohol, a polyalkoxylated sulfate salt and a polyalkoxylated sulfosuccinate salt, and wherein the second active ingredient is effective in substantially inhibiting the production of exoprotein from Gram positive bacteria.

Claim 1 is patentable over the combination of Stolar and D'Augustine for the reasons set forth above. Therefore, claims 14-25, which depend from claim 1, are patentable over the combination of Stolar and D'Augustine for the same reasons as claim 1 above. In particular, there is no motivation to combine the phenoxyethanol as disclosed in Stolar with the devices of

D'Augustine to arrive at each and every limitation of claim 1.

The Syverson reference does not overcome this deficiency. Specifically, Syverson is merely directed to absorbent articles, such as catamenial tampons, which include an effective amount of an ether compound to substantially inhibit the production of exotoxins by Gram positive bacteria. Significantly, nowhere in Syverson is a first active ingredient as set forth in claim 1 even mentioned, much less that such a compound has antimicrobial properties or is effective in inhibiting the production of exoprotein from Gram positive bacteria.[6]

As such, claims 14-25 are patentable over the combination of Stolar, D'Augustine, and Syverson.

[6] Syverson furthermore fails to disclose or suggest a non-absorbent substrate selected from the group consisting of a non-absorbent incontinence device, a barrier birth control device, a tampon applicator, and a douche, but rather is directed solely to absorbent articles.

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K-C 16,858.1
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Conclusion

In view of the above, Applicants respectfully request favorable reconsideration and allowance of all pending claims. The Commissioner is hereby authorized to charge any fee deficiency in connection with this Letter To Patent And Trademark Office to Deposit Account Number 19-1345 in the name of Senniger, Powers, Leavitt & Roedel.

Respectfully Submitted,

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